

The analogy here is that personal computers went from a hobbyist novelty to a broader adoption in the home/office when software applications likes spreadsheets/wordprocessors were developed. Similarly, for new technologies to be useful for chemical safety, there will need to be advances in regulatory policy (i.e., the "software" of the toxicology world).



Highlights of a Few Scientific and Policy Advances at EPA







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- Technology advances to comprehensively evaluate large numbers of chemicals across toxicological space
- Strategies for incorporating alternative methods in regulatory decisions
- Incorporating alternative methods in identifying potential candidates for prioritization
- Managing and integrating diverse data using visualization and decision support tools



Toxicology is Analogous to Trying to Create a 'Picture of Everything'



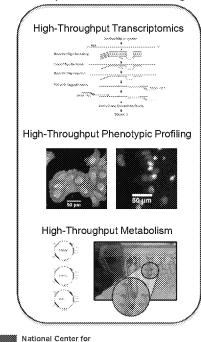
Picture of Everything Howard Hallis

- In 1997 an artist named Howard Hallis started drawing a 'Picture of Everything', it took 13 years to complete, stands at 15 x 14 feet.
- The ideal toxicity testing approach provides comprehensive coverage of relevant toxicological responses
- It should identify the mechanism/mode-ofaction (with dose-dependence)
- It should identify responses relevant to the species of interest and include consideration of metabolism (detoxification/bioactivation)
- Responses should ideally be translated into tissue-, organ-, and organism-level effects
- · It must be economical and scalable

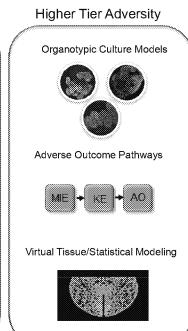


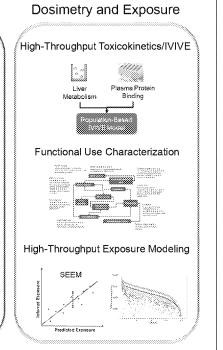
A Portfolio of Scientific Advances in Toxicity Testing at EPA

Comprehensive Screening

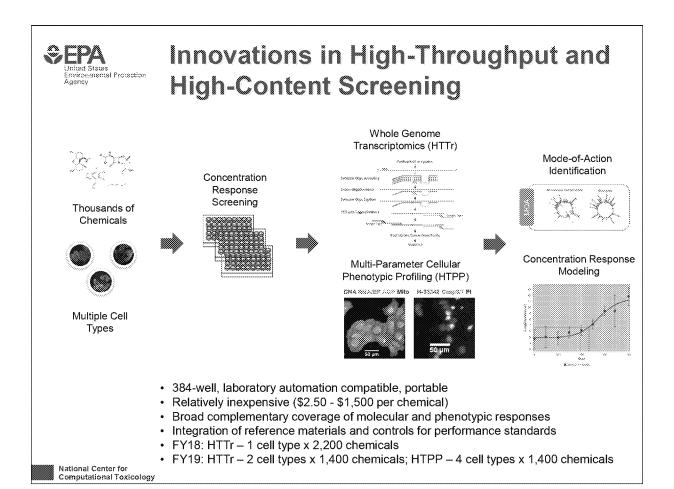


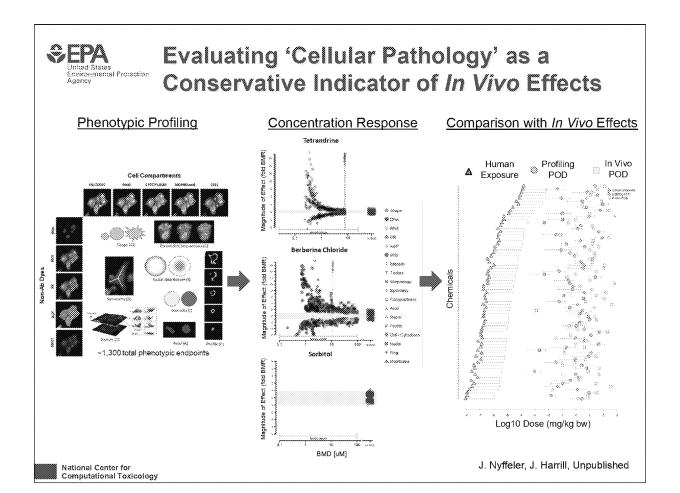
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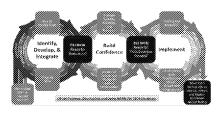






A Strategic Plan to Develop and Integrate Alternatives in TSCA





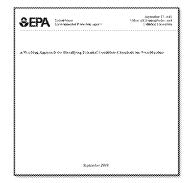
https://www.epe.gov/eissessing.and-managingchemicals-under-tsoa/alternative-test-methods-andstrategies-raduce

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- Amended TSCA requires "Scientifically valid test methods and strategies that reduce or replace use of vertebrate animals while providing information of equivalent or better scientific quality and relevance that will support regulatory decisions" Section 4(h)(1)(B)
- Three main parts
 - · Identify, develop, and integrate alternatives
 - · Establish relevance, reliability, and confidence
 - · Training, education, and collaboration
- Near-term (0 3 yr), intermediate (3 5 yr), and long-term objectives (>5 yrs)
 - Ex: Identify and maintain a list of most requested studies for new and existing chemicals under TSCA
- Long term goal is to "reduce and eventually eliminate vertebrate animal testing"



Incorporating Alternatives to Identify Candidates for Prioritization



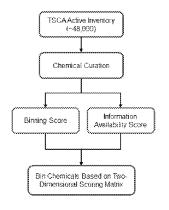
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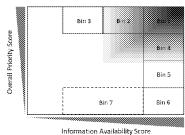
risk-avaluation

- Purpose to develop and describe approaches to identify a pool of potential candidates that will inform selection of low and high priority candidates for prioritization
- Two approaches
 - Near-term approach Identify 20 high and 20 low priority candidates by March 2019
 - Long-term approach Identify high and low priority candidates beyond 2019
- Alternatives primarily integrated in long-term approach
- Prioritization is a formal 9 12 month process followed by risk evaluation for high priority substances
- High priority substances must have sufficient information for risk evaluation to be completed in 3 years



Characteristics of Proposed Long-Term Approach for Candidate Identification





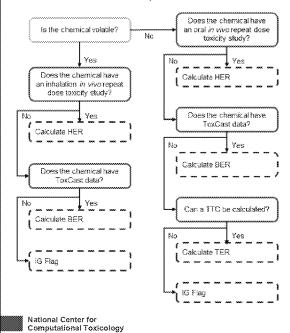
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- Long-term approach proposes to bin chemicals based on a combination of risk-related scoring and information availability to inform priority candidate selection
- Risk-related scoring considers human hazard, exposure, genotoxicity/carcinogenicity, ecological hazard, susceptible populations, and persistence/bioaccumulation
- Information availability scoring considers portfolio of potentially relevant human health and ecological toxicity information for risk evaluation
- Relies on a large data management infrastructure and decision support tools that store and integrate information from alternatives as well as traditional toxicology, exposure, and environmental faterelated studies.



Example of Integrating Alternatives in Long-Term Approach

Proposed Human Hazard and Exposure Ratio Component



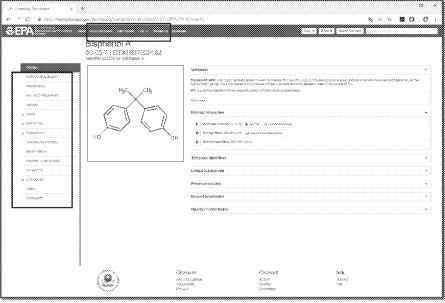
- Tiered process uses traditional in vivo toxicity information when available, but considers in vitro bioactivity and threshold of toxicological concern (TTC) as second and third tier sources
- EPA ExpoCast high-throughput exposure modeling provides risk-based context to quantitative hazard values
- Component score based on magnitude of the hazard-, bioactivity-, or TTC-toexposure ratio

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Enabling Translation Through Data Visualization and Decision Support Tools

EPA Comptox Chemicals Dashboard



https://comptox.epa.gov/dashboard/

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Take Home Messages...







- Advancing toxicology to the new and improved version will require both scientific and policy advances
- New technologies exist for rapidly and comprehensively covering toxicological space at significantly less cost
- New strategies provide a blueprint for developing and integrating alternatives for regulatory decisions related to statutes like TSCA
- Alternatives are a key component of the long-term strategy for informing priority candidate selection in **TSCA**
- Data management systems and decision support tools will be increasingly important for interpreting and integrating the expanding and diverse landscape of chemical safety information

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Acknowledgements and Questions

EPA Colleagues:

NCCT

NERL

NHEERL

NRMRL

NCEA

OCSPP

Collaborative Partners:

NTP

FDA

NCATS

Health Canada

ECHA

JRC

EFSA

A*STAR

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